Sub B2
Cl 4
B
1

2. (Twice amended) The fusion of claim 1 wherein E1 and E2 are selected from the group consisting of beta-ketothiolase (phbA) and acyl-CoA reductase (phbB); phbB and phbA; [PHA] polyhydroxyalkanoate synthase (phaC) and phasin (phaP); phaP and phaC (1D); phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC.

Remarks

Information Disclosure Statement

Additional copies of the references filed with the Information Disclosure Statement mailed on January 11, 2000, will be submitted shortly.

Oath/Declaration

A substitute Declaration of Inventorship will be submitted shortly..

Claim Objection

Claim 2 was objected to under 37 CFR 1.75(c) for allegedly failing to further limit the subject matter of claim 1. The applicants respectfully disagree. In claim 1, a protein fusion can be formed from E1 and E2 which can be independently selected from the enzymes enumerated therein. In claim 2, the protein fusion is further limited to the ones formed of the E1 and E2 pairs enumerated in the Markush group. A simple mathematical calculation shows that the number of fusion proteins encompassed in claim 1 would be much larger than that provided in claim 2. Therefore, claim 2 further limits the subject matter of claim 1.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-3, 5 and 6 were rejected under 35 U.S.C. § 101 as allegedly directed to non-

statutory subject matter. The applicants respectfully disagree. The Examiner asserted that the rejected claims are drawn to a product of nature and, thus, are not patentable. However, as one of ordinary skill in the art would appreciate, a protein fusion of two enzymes that exist separately in nature is a new enzyme which does not exist in nature.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-6 were rejected as indefinite under 35 U.S.C. § 112, second paragraph. The Examiner stated that the term "PHA" is indefinite. The applicants respectfully disagree. The term "PHA" is used routinely in the art to denote polyhydroxyalkanoate (see the references cited in the Office Action, *infra*). Similarly, PHB is used to denote poly(3-hydroxybutyrate). However, to facilitate prosecution, claims 1 and 2 have been amended to recite the full name of the polymers. Support is found at least in the original claims.

Rejections under 35 U.S.C. §103(a)

Claims 1-3 and 6 were rejected under 35 U.S.C § 103 as obvious over Bulow et al., "Multienzyme systems obtained by gene fusion," in TIBTECH 9:226-231 (1991) ("Bulow") in view of Peoples et al., "Biosynthetic thiolase from *Zoogloea ramigera*," in J. Biol. Chem. 262:97-102 (1987) ("Peoples 1987") and Peoples et al., "Fine structural analysis of the *Zoogloea ramigera* phbA-phbB locus encoding b-ketothiolase and acetoacetyl-CoA reductase: nucleotide sequence of phbB," in Mol. Microbiol. 3:349-357 (1989) ("Peoples 1989"). Claim 4 was rejected under 35 U.S.C § 103 as obvious over Bulow in view of Peoples 1987 and Peoples 1989 as applied to claims 1-3 and 6 and further in view of Argos, "An investigation of oligopeptides linking domains in protein tertiary structures and possible candidates for general gene fusion," in

J. Mol. Biol. 211:943-958 (1990) ("Argos"). Claim 5 was rejected under 35 U.S.C § 103 as obvious over Bulow in view of Peoples 1987 and Peoples 1989 as applied to claims 1-3 and 6 and further in view of U.S. Patent No. 5,610,041 to Somerville et al. ("Somerville"). These rejections are respectfully traversed.

Bulow

Bulow describes a β-galactosidase-galactokinase protein fusion that catalyzes sequential catalytic steps, 1) the hydrolysis of lactose to glucose and galactose, followed by 2) phosphorylation to galactose-1-phosphate (p. 228, Fig. 3). Bulow describes **generally** the advantages of a fusion protein, such as its capability to catalyze sequential steps, facilitated purification, favorable enzyme kinetics and proximity effects (p. 226). Bulow also describes **generally** the requirement of a short linker (two to ten amino acid residues) to form a fusion protein (p. 230). However, as the Examiner correctly acknowledged, Bulow does not teach a fusion protein formed of two enzymes as provided in claim 1 of the present application or their expression in a bacteria.

Peoples 1987

Peoples 1987 describes the cloning, nucleotide and amino acid sequences of *Zoogloea ramigera* β-ketothiolase (p. 99, right column, bottom) and expression in *E. coli*.

Peoples 1989

Peoples 1989 discloses the cloning, nucleotide and amino acid sequences of *Zoogloea ramigera* acetoacetyl CoA reductase and expression in *E. coli* (p. 353-354).

Argos

Argos is a computational study of the oligopeptides linking protein domains and states that pentapeptides with only glycine, serine **and** threonine can be good linkers (p. 947, left column, middle). Argos, therefore, does not disclose a linker formed of glycine-serine.

Somerville

Somerville discloses expression of separate β-ketothiolase or acetoacetyl CoA reductase in *Arabidopsis thaliana*. As the Examiner corrected noted, Somerville does not teach construction or expression of any fusion protein.

The Claimed Invention

Claims 1 and 3-6 are drawn to a protein fusion which specifically requires two enzymes that are listed in the Markush group be fused via a linker formed of amino acids. Claim 2 further requires the two enzymes which are fused be the pairs of enzymes as provided therein.

As the discussion of the cited art references shows, the cited art references, in combination, fail to disclose every element of any of claims 1-6 of the present application. Even if one were to argue that the cited references, in combination, disclose every element of any of

claims 1-6, the subject matter of claims 1-6 is still not obvious over the cited art references. It is well established that, in order to make a proper § 103 rejection, the cited references have to provide the motivation or suggestion leading one of ordinary skill to the claimed subject matter (See MPEP § 2143). Such a motivation cannot be based on the knowledge provided by the applicants' disclosure. Application of McLaughlin, 443 F.2d 1392, 1395 (CCPA 1971). Further, even if such motivation or suggestion exists, there has to be a reasonable expectation of success, as determined by one of ordinary skill in the art, of the claimed subject matter (See MPEP § 2143.02).

As discussed above, Bulow discusses **generally** the advantages of a fusion enzyme. The general advantages of a fusion enzyme as compared to separate enzymes are within the knowledge of those skilled in biotechnology. However, Bulow does not provide the motivation to fuse enzymes for the manipulation of biosynthetic pathways of PHA production. One of ordinary skill in the art would appreciate that the fusion of enzymes for PHA production requires a specific understanding of the biosynthetic pathways of PHA production. As such, a general discussion of advantages in a field in general does not provide the motivation which would lead one of ordinary skill in the art to the subject matter of claims 1-6. To hold otherwise would render any specific findings in a field to be patentably meaningless because, as one of ordinary skill in the art would appreciate, for one to start a research activity in a specific area in the field, it is a prerequisite that he or she has a general understanding of some advantages known in the field which may exist in certain area. Scientific findings as a result of serendipity, if any, are exceptionally rare. One certainly can not argue that only scientific findings of serendipity are

patentable. As such, Bulow does not provide specific motivations for the subject matter of claims 1-6.

Peoples 1987 and Peoples 1989 disclose only sequence studies of the genes and amino acids of *Zoogloea ramigera* β-ketothiolase and acetoacetyl CoA reductase. Peoples 1987 and Peoples 1989, therefore, do not provide the motivation which would lead one of ordinary skill in the art to combine the references to yield the subject matter of claims 1-6.

Argos only identifies potential linking domains in protein tertiary structures. Argos, therefore, does not provide the teaching leading one of ordinary skill in the art to combine the references to form the subject matter of claims 1-6.

Somerville discloses only transgenic plants encoding separate and free enzymes. The statement in Somerville that there is an advantage of producing PHA/PHB in genetically engineered plants by reducing cost of production is not a motivation which would lead one of ordinary skill in the art to a protein fusion of claims 1-6.

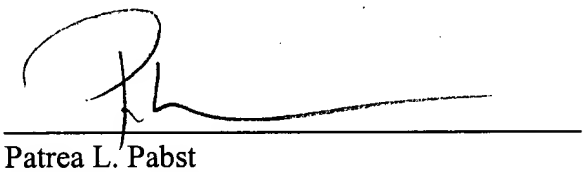
Therefore, none of the cited references provide any specific motivation which would lead one of ordinary skill in the art to a protein fusion for the production of PHA as claimed in claims 1-6. Further, even if one were to argue that one of the cited art references provides such a motivation exists, one of ordinary skill in the art sill can not have a reasonable expectation of success of the subject matter of claims 1-6. As discussed above, a **general** discussion of certain advantages in a field in general in Bulow can not lead one of ordinary skill in the art to have a reasonable expectation of success of the subject matter of claims 1-6 absent a specific understanding of the biosynthetic pathways of PHA production. Further, none of Peoples 1987,

Peoples 1989, Argos and Somerville teaches a fusion protein. As such, none of Peoples 1987, Peoples 1989, Argos and Somerville can lead one of ordinary skill in the art to have a reasonable expectation of success of the subject matter of claims 1-6.

In summary, claims 1-6 are not *prima facie* obvious over the cited references. Therefore, the rejections of claims 1-3 and 6 as obvious over Bulow in view of Peoples 1987 and Peoples 1989, claim 4 as obvious over Bulow in view of Peoples 1987 and Peoples 1989 as applied to claims 1-3 and 6 and further in view of Argos, and claim 5 as obvious over Bulow in view of Peoples 1987 and Peoples 1989 as applied to claims 1-3 and 6 and further in view of Somerville, are inappropriate.

Allowance of all claims 1-28, 31, 35-39, 41-49 and 51-52 is earnestly solicited. All claims as pending are attached in an appendix for the convenience of the Examiner.

Respectfully submitted,



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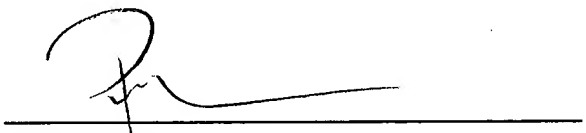

Patrea Pabst

Date: March 29, 2001

Appendix I: Marked Up Claims as Pending Upon Entry of the Amendment

1. (Twice amended) A protein fusion having a formula selected from the group consisting of E1-L_n-E2 and E2-L_n-E1, wherein E1 and E2 catalyze successive reactions in a [PHA] polyhydroxyalkanoate biosynthetic pathway and are each selected from the group consisting of β-ketothiolases, acyl-CoA reductases, [PHA] polyhydroxyalkanoate synthases, [PHB] poly(3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferase, in which linker L_n is a peptide of n amino acids that link E1 to E2 or E2 to E1.

2. (Twice amended) The fusion of claim 1 wherein E1 and E2 are selected from the group consisting of beta-ketothiolase (phbA) and acyl-CoA reductase (phbB); phbB and phbA; [PHA] polyhydroxyalkanoate synthase (phaC) and phasin (phaP); phaP and phaC (1D); phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC.

3. The fusion of claim 1 wherein n in the linker is between zero and 50 amino acids.

4. The fusion of claim 1 wherein the linker is glycine-serine.

5. The fusion of claim 1 expressed in a plant.

6. The fusion of claim 1 expressed in a bacteria.

Appendix II: Clean Copy of Claims as Pending Upon Entry of the Amendment

1. A protein fusion having a formula selected from the group consisting of E1-L_n-E2 and E2-L_n-E1, wherein E1 and E2 catalyze successive reactions in a polyhydroxyalkanoate biosynthetic pathway and are each selected from the group consisting of β-ketothiolases, acyl-CoA reductases, polyhydroxyalkanoate synthases, poly(3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferase, in which linker L_n is a peptide of n amino acids that link E1 to E2 or E2 to E1.

2. The fusion of claim 1 wherein E1 and E2 are selected from the group consisting of beta-ketothiolase (phbA) and acyl-CoA reductase (phbB); phbB and phbA; polyhydroxyalkanoate synthase (phaC) and phasin (phaP); phaP and phaC (1D); phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC.

3. The fusion of claim 1 wherein n in the linker is between zero and 50 amino acids.

4. The fusion of claim 1 wherein the linker is glycine-serine.

5. The fusion of claim 1 expressed in a plant.

6. The fusion of claim 1 expressed in a bacteria.